JUVENILE HYPOTHYROIDISM

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'Juvenile hypothyroidism' is a generic title for a group of diseases arising from a variety of causative factors and characterized by subthyroidism with apparent onset in childhood. The term 'cretinism' in this paper is reserved for those cases which show gross hypothyroidism with signs

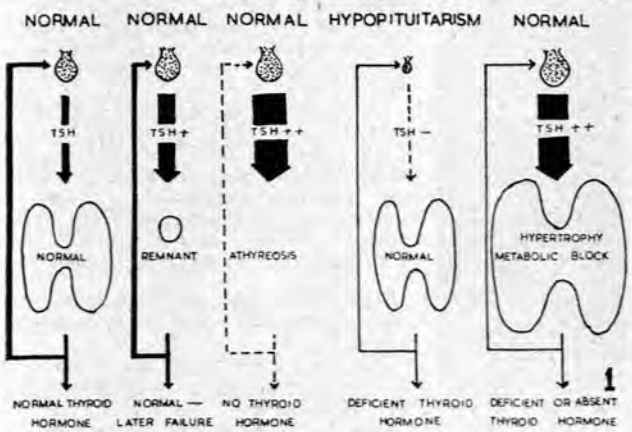

Fig. 1. Simple diagrammatic representation of aetiological factors in hypothyroidism.

of mental deficiency and with onset at birth, or very soon after. Because of the variety of types and of aetiological factors (Fig. 1)—often unknown—it might be better to refer to the cases as belonging to the broad group comprising juvenile hypothyroid syndromes.

Five cases are presented, with a brief functional classification of hypothyroidism in childhood and adolescence, and a discussion on differentiating features.

CASE REPORTS

Case 1. European female aged 14 years

This patient was referred for investigation by her mother because of failure to grow. Pregnancy and delivery had been normal and she had passed all her milestones at the expected times. She started school at the age of 7 and made good progress; in fact, the year before attending at hospital had come top of her class. However, from about the age when she first attended school it became gradually apparent that she was not growing normally and, in addition, she often complained of feeling cold.

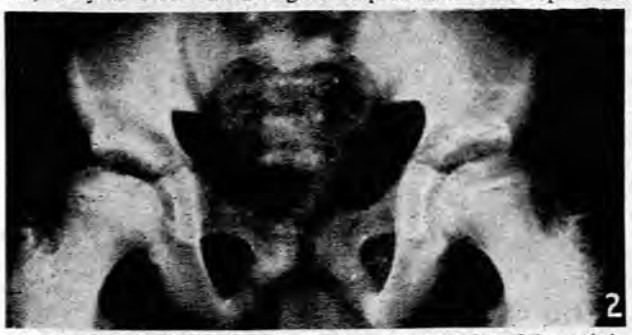

Fig. 2. Case 1. X-ray of pelvis. Note the fragmentation of the capital femoral epiphyses and of the epiphyses of the trochanters.

On examination, she was found to be a quiet, short (52 inches), obese child with a dry, scaly skin. There was no evidence of secondary sexual development. The sleeping pulse rate was 60 beats per minute and her thyroid was not palpable. The rest of the physical examination was normal. Her bone age was estimated to be 13 years (Fig. 2).

The electrocardiograph (ECG) showed low voltage QRS complexes under 10 mm. in leads V4-V6, and flattened T-waves (Fig. 3). The serum cholesterol was 636 mg.%. The basal metabolic rate BMR was −52%.

Treatment was begun with 10 μg. of tri-iodothyronine twice daily for 7 days and then continued with 0·1 mg. of L-thyroxine twice a day. Within a week the ECG showed increased voltage

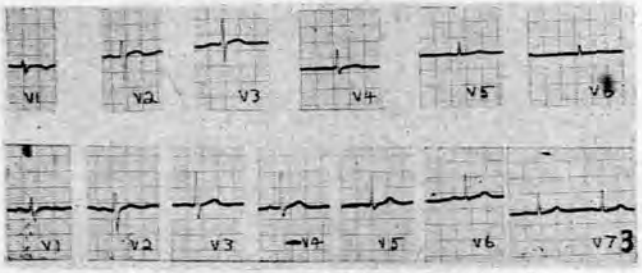

Fig. 3. Case 1. Upper tracings = ECG taken on admission. Lower tracings = ECG taken after treatment with tri-iodothyronine for 1 week. Note the increasing voltage of the T-waves in the left praecordial leads.

and higher T-waves (Fig. 3) and there was marked subjective improvement. Four months later she had grown 2 inches, her breasts had begun to develop (Figs. 4A and 4B), the sleeping pulse rate was now 84 beats per minute, and the BMR was −3%.

Case 2. Coloured male aged 18 years

This patient presented himself at medical out-patients with the complaints that he was too short and was much slower than his friends of the same age. He had had no schooling and was unable to give a detailed history or produce any reliable witnesses. He said he always felt cold.

On examination he lay in bed completely covered by blankets on a warm day. He was short (53 inches with a span of 50 inches) and obese and had a thick, dry skin; coarse facial features (Figs. 5A and 5B). His pulse rate at rest was 46 beats per minute. There was a nodular goitre affecting mostly the right lobe and the isthmus. The rest of his physical examination, including secondary sex characters, was normal.

It was not possible to obtain an accurate estimation of his intelligence but, taking into account his social background and lack of formal schooling, he appeared to be of low normal intelligence.

His bone age was estimated to be 13-15 years.

The ECG was within normal limits. The serum cholesterol was 269 mg.%. The BMR was −30%.

Treatment was begun with 10 μg. of tri-iodothyronine twice daily and within a week it became apparent that there was improvement. He no longer lay in bed curled up beneath the blankets; he was active, alert and helpful about the ward. His resting pulse rate had risen to between 80 and 90 beats per minute. He was discharged on a maintenance dose of 0·1 mg. of L-thyroxine twice daily.

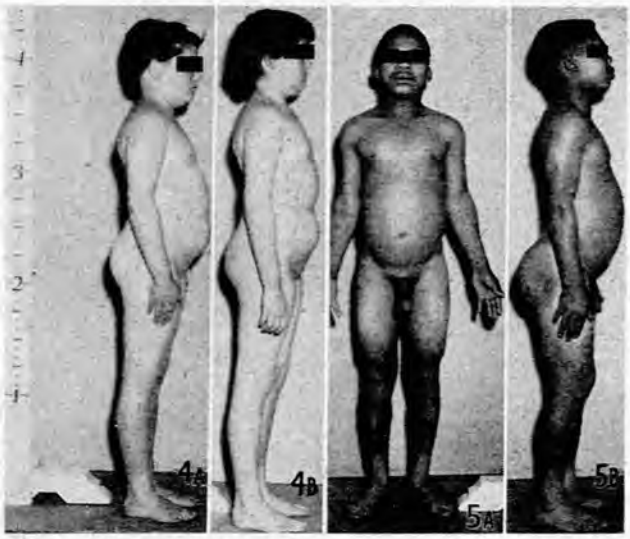

Fig. 4A. Case 1. Before treatment.
Fig. 4B. Case 1. After treatment for 4 months with thyroid hormone. Note change in profile.
Figs. 5A and 5B. Case 2.

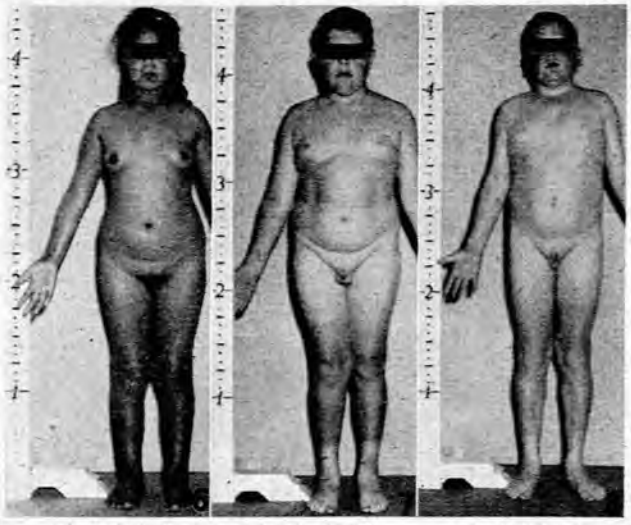

Fig. 6. Case 3.

Fig. 7. Case 4.

Fig. 8. Case 5.

Case 3. Coloured female aged 19 years

This patient attended at medical out-patients complaining of shortness of stature, of a swelling in the neck which had been present about 5 years, and of increasing obesity. Her mother stated that her milestones, following a normal pregnancy and delivery, had all been normal. When she first attended school at the age of 6 her height had been normal for her age. She was able to read at 7 years. Dating from this time she failed to grow and her performance at school deteriorated. She eventually passed standard 4 at 14 years and then left school. The rest of her family were all normal, except for her mother, who had a multinodular non-toxic goitre. She had begun to menstruate only 1 month before attending at hospital.

On examination she was found to be short (51 inches) and obese (Fig. 6), with a thick, dry skin and a hoarse voice. There was no body hair. The breast development was fair, but on palpation seemed to be mainly fat. There was a large cystic mass in the upper pole of the right lobe of the thyroid.

Her bone age was estimated to be 13-14 years.

The ECG was within normal limits. The serum cholesterol was 325 mg.% before treatment.

She was treated as an out-patient with 0·1 mg. of L-thyroxine twice a day and made steady progress. She became brighter, lost weight and had more energy. The thyroid swelling gradually decreased and eventually disappeared within 3 months. One year later she had grown 1½ inches, but her voice was still hoarse and she still had no pubic hair, although her periods were now lasting 4 days instead of 1 day, and she showed good development of her nipples.

Fig. 9. Case 4. X-ray of spine. Note the absence of secondary ossification centres.

Case 4. European male aged 15 years

The complaints in this case were of mental dullness and failure to grow. The patient weighed 10½ lb. at birth, after a normal pregnancy and delivery. His mother stated that he passed all his milestones at the expected times and by 2 years was walking and talking normally. From this time, however, he made no further progress and at the age of 3 years was started on 'thyroid'. No illness of any sort had been noted and no swelling in the neck had been observed. For a period of 1 year before his visit to hospital he had not had any thyroid preparation. The rest of his family were all normal and tall.

On examination he was found to be short (55 inches) and obese (Fig. 7), with many brown moles. The skin was dry and tended to crack. There was no secondary sexual development. The rest of the physical development was normal and the thyroid was not palpable. His bone age was estimated at 9 years (Figs. 9 and 10).

The ECG showed bradycardia and flattened T-waves. The serum cholesterol was 425 mg.%.

He was treated as an out-patient with 0·1 mg. of L-thyroxine twice daily. When examined on subsequent visits he was much more alert and active, and an ECG done later was now within normal limits.

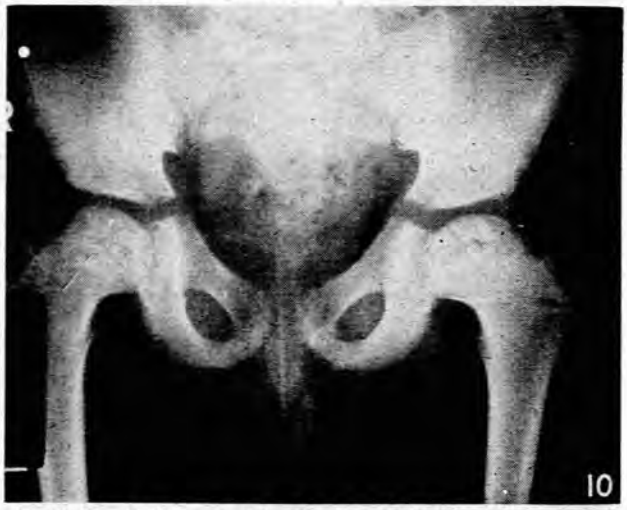

Fig. 10. Case 4. X-ray of pelvis. Note the delay in closure of acetabulum, the small epiphyses, and the fragmentation (epiphyseal dysgenesis) of the epiphyses of the lesser trochanters and of the capital femoral epiphyses.

Case 5. European male aged 17 years

In 1950 at the age of 9 years this patient underwent a craniotomy for a craniopharyngioma. He had developed normally in physique and intelligence at this stage. The operation was successful and he was able to lead a normal life, except that he failed to grow, developed no secondary sex characteristics, and suffered from polydipsia and polyuria.

On examination he was found to be a bright and cooperative young boy who measured 57 inches in height. He was obese

and there was complete absence of secondary sex development (Fig. 8). His resting pulse rate was 90 beats per minute. There was bitemporal hemianopsia and the optic discs were atrophic. The thyroid was normally palpable and the rest of the physical examination was essentially normal. Skull X-ray showed the typical suprasellar calcification of a craniopharyngioma.

His bone age was estimated to be between 13 and 14 years.

The ECG was within normal limits. The serum cholesterol was 230 mg.%. The BMR was −22%. The protein-bound iodine (PBI) was 2·6 μg. per 100 ml. (normal range 4-8 μg. per 100 ml.).

Treatment was begun with 0·1 mg. of L-thyroxine twice daily, together with 5 mg. of prednisone daily and pitressin tannate as required.

SUMMARY OF THE 5 CASES

	Case 1	*Case* 2	*Case* 3	*Case* 4	*Case* 5
Age (yrs.)	14	18	19	15	17
History of previous development	Normal up to ± 7 yrs.	Not available	Normal up to ± 6 yrs.	Normal up to 2 yrs.	Normal up to 9 yrs.
Epiphyseal dysgenesis	Yes	Yes	No	Yes	No
Height (inches)	52	53	51	55	57
Obese	Yes	Yes	Yes	Yes	Yes
Secondary sex development	No	Normal	Late	No	No
Thyroid	Not palpable	Goitre	Nodule	Not palpable	? Normal
ECG	Abnormal	Normal	Normal	Abnormal	Normal
BMR	−52%	−30%	—	—	−22%
Serum cholesterol before treatment	mg.% 636	mg.% 269	mg.% 325	mg.% 425	mg.% 230
PBI	—	—	—	—	2·6μg.%
Bone age (yrs.)	13	13-15	13-14	9	13-14
Aetiology	Acquired ? thyroid atrophy	Non-endemic goitrous hypothyroidism	Partial athyreosis (mid-line remnant)	Acquired ? thyroid atrophy	Secondary to hypopituitarism

CLASSIFICATION OF SUBTHYROIDISM IN EARLY LIFE

The division is broadly congenital hypothyroidism and acquired hypothyroidism; there may be some overlapping of aetiological factors.

Early (congenital) Hypothyroidism

1. *Anatomic Dysgenesis*

There is in this category an embryonic defect in the development of the thyroid, which may be completely absent (athyreosis) or may be represented by small functioning remnants in the neck or attached to the tongue. It has been shown that these 'remnants' are hyperfunctioning.[1] In the latter case the infant may be normal at birth and remain so for a period until the overstressed remnant atrophies and the child becomes hypothyroid. In the former case the condition of hypothyroidism with cretinism will certainly be manifest unless treatment is begun soon. Often despite timely and adequate treatment the infant will be mentally defective with good physical development. It is thought that the lack of development of the brain may begin *in utero*, although Stanbury and Querido[2] suggest that there may be an associated mental defect in some of these cases.

The foetal thyroid becomes a functioning structure by the 12th week of gestation and supplies sufficient thyroid hormone for the needs of the foetus.[3,4] This fact, together with the study of retarded skeletal development in the newborn, enables an estimate to be made of the time of onset of intra-uterine failure of thyroid hormone.

It is estimated that 45% of athyreotic babies adequately treated before the age of 6 months have attained the range of normality in mental development. The prognosis in individual cases is difficult and variable.

2. *Nutritional Hypothyroidism* (*endemic goitrous hypothyroidism or cretinism*)

This disease occurs in environments where there is lack of iodine. Well-known areas are the Alps and the Himalayas.

A typical case occurs in a family with progressively severe goitres, producing finally a goitrous, mentally deficient infant. The thyroid may undergo atrophy early. It is thought by some observers that these babies are functionally athyreotic, thus explaining the high incidence of mental deficiency or cretinism. Stanbury and Querido[2] suggest that a genetically inborn error of metabolism may be accentuated by iodine lack in the environment (see below). This would help to explain why not all infants are affected despite widespread iodine lack. A high uptake of ^{131}I shows the avidity of the thyroid for iodine. Urine ^{127}I is low.

3. *Inborn Errors of Metabolism* (*non-endemic familial goitrous hypothyroidism*)

The synthesis of thyroid hormone has been subject to detailed study. It is a complex process involving several enzyme systems in successive steps leading to the final principles. Failure of an enzyme system at any point in the chain can and does occur, with resultant deficient thyroid hormone.

Three main types of familial hypothyroidism, as follows, have been studied, characterized by a specific enzyme failure at a particular stage. All the patients, either early or in later years, have an enlarged hyperplastic thyroid gland.

(*a*) *Failure in the organification of iodide.* The gland may take up iodine but is unable to oxidize it to elemental iodine in the absence of an oxidase which is normally present.[5]

(*b*) *A postulated failure of coupling of iodotyrosines.* Thyroxine is formed when 2 molecules of di-iodothyronine are coupled; 3-3′-di-iodothyronine is formed by coupling of 2 molecules of mono-iodotyrosine; and so forth. Cases have been described with large goitres and mental retardation and with large amounts of mono- and di-iodotyrosine in the thyroid but only low peripheral concentration of thyroxine.[6]

(*c*) *Lack of de-iodination of iodotyrosines.* Thyroglobulin normally undergoes proteolysis with the release of thyroxine, tri-iodothyronine and mono- and di-iodotyrosine. The last two substances are de-iodinated by a specific enzyme in the thyroid[7] and do not appear in the blood.

Three cases of goitrous hypothyroidism have been described that were unable to de-iodinate di-iodotyrosine. Two were cretins, one was normal. When these cases were given intravenous injections of labelled di-iodotyrosine it appeared unchanged in the urine, whereas in normal people it did not appear in the urine.[7]

The causative factor here seems to be a loss in hormone precursors. The familial incidence in this type is high.

4. *Congenital Goitres with Hypothyroidism*

In babies whose mothers have received drugs such as thio-uracil, iodides, etc., goitres may be present at birth, as well as cretinism. After birth the goitres usually disappear and the infants may be toxic, euthyroid or hypothyroid.[8-10] Retarded osseous development and epiphyseal dysgenesis may provide evidence of intra-uterine hypothyroidism.

There remain some cases in this group in which the aetiology is obscure. The infants who are hypothyroid at birth may remain so and should be treated if this occurs.

Later (acquired or minor congenital) Hypothyroidism

(In these cases there must be evidence of preceding normal thyroid function.)

1. *Juvenile Hypothyroidism* (*'Juvenile myxoedema'*)

There are a number of causative factors, some of which have already been discussed, viz. partial athyreosis, infective or infiltrative diseases, and thyroiditis, including Hashimoto's disease in children, or primary failure of the thyroid.

The term 'juvenile myxoedema' should be reserved for those cases which in addition have the typical skin changes as in their adult counterpart. Often these patients are of normal intelligence and may not even appear as sluggish as the adult with myxoedema.

The onset of the disease is characteristically insidious, with gradual slowing of growth and activity followed at a later stage by a more abrupt failure of growth.

The thyroid stimulating hormone (TSH) levels are reported as being high in this group.[11]

2. *Secondary Hypothyroidism*

This group comprises cases which have inadequate thyroid function secondary to pituitary failure, either as a specific failure of TSH or as part of the syndrome of panhypopituitarism. In these cases it may be demonstrated that the TSH levels are low and that the thyroid is capable of responding to TSH stimulation unless the gland has become severely involved. Severe involution is seldom present and repeated stimulation by exogenous TSH will usually produce adequate thyroid response.

The diagnosis may present some difficulties, because the symptoms are usually mild and the skin changes of juvenile myxoedema absent. The main problem is to differentiate the disease from dwarfing due to deficiency of growth hormone or hypopituitarism, for the two conditions may co-exist.

Wilkins[12] points out that in dwarfing due to hypothyroidism the skeletal proportions are infantile, whereas in dwarfing due to lack of growth hormone the proportions are adult.

As in the previous categories the bone age is retarded, and this can be accelerated by the exhibition of thyroid. Thyroid will not increase the stature in deficiency of growth hormone.

The PBI estimation is useful; the level of this is always low, provided the usual precautions are taken.

Finally radio-active iodine studies may be utilized, particularly in combination with TSH stimulation, to establish the existence of normal potential thyroid function.

DISCUSSION

Wilkins[15] states that hypothyroidism is one of the commonest of all endocrine disorders of childhood and adolescence in the United States of America. There is a wide range in the spectrum of the disease, the clinical manifestations of which are directly proportional to the amount of thyroid hormone produced and inversely proportional to the age of onset of thyroid dysfunction. At the one end of the scale there is the floridly myxoedematous cretin—cold, sluggish, with coarse facial features, and markedly stunted. At the other end of the scale there is the mildly hypothyroid patient whose main complaint is of failure to grow satisfactorily.

Diagnostic Features

The gross examples of the disease are adequately described in the text-books and need no further amplification. Difficulty may arise with the mild cases and for this reason a few points are worth emphasizing.

Bone changes. Most observers lay considerable stress on retarded osseous development. The skeletal system in children is most sensitive to thyroid deficiency. The bone age is always retarded unless thyroid failure is of recent onset.[13,14] Delay in the appearances of epiphyseal centres, primary and secondary, plus irregular ossification of the epiphyses—epiphyseal dysgenesis—which gives rise to an irregular stippling in the radiograph, is practically pathognomonic of hypothyroidism.[12,15] This is not a reported feature of secondary hypothyroidism. However, the radiological appearance of osteochondritis deformans is sometimes very similar, although in it there is no evidence of retarded osseous development. The hip joints, the epiphyses of the knee, the wrist joints and the femoral trochanters may be affected. Jackson *et al.*[16] drew attention to the vertebral bodies, which are 'unusually small, square and dense, with irregular outlines'. They also point out that occasionally one vertebra may be particularly small, wedge-shaped and displaced backwards. The latter features are also seen in gargoylism. The failure of the appearance of the vertebral secondary ossification centres is partly responsible for the short stature.

The serum cholesterol is usually high in the untreated cases except in the secondary hypothyroidism of hypopituitarism, when it may be normal.

Electrocardiograph. The ECG changes are very valuable, both in the diagnosis and in the evaluation of the efficacy of therapy. The usual changes are a prolonged P-R interval and low voltage QRS complexes and flattened T-waves. Bradycardia is frequently mentioned as an additional feature, and in this respect it is interesting to note the two cases of adult cretins reported by Jackson[17] with pulse rates above normal. Benda and Falta[18] state that tachycardia is a recognized occasional feature of infantile cretinism.

Sexual features. The development of secondary sexual features is usually delayed, but not necessarily so.[17] Case 2 had normal development of sex characteristics, with a large penis. Jackson[17] states that in male adult cretins the penis and testicles may be outsize. Case 3 menstruated and while on treatment, the duration of her menses increased from 1 day to 4.

The circulating thyroid hormone was estimated indirectly by measuring the PBI, which is always low in hypothyroidism. It must be remembered that the administration of iodides *in any form* may result in high values. The normal range is 4-8 μg.%. Case 5 had a PBI of 2·6 μg. % and with the

exception of the skeletal changes this was the best objective evidence of hypothyroidism.

Basal metabolic rate. The BMR may be misleading, although in most cases of hypothyroidism it is singularly low.

Radio-active iodine studies are used to establish the presence—or absence—of functioning thyroid tissue by direct scanning methods over the neck. In addition, the metabolic turnover and synthesis of the thyroid hormones can be investigated. In nutritional goitrous hypothyroidism most cases will take up ^{131}I quite rapidly with a subsequent slow rise in the protein-bound ^{131}I, whereas in the non-endemic goitrous hypothyroid patients (metabolic disorders) ^{131}I may be taken up quite avidly in some cases, but because they cannot manufacture thyroid hormones adequately there will be no significant rise in the protein-bound ^{131}I.

Therapy and response. The response to therapy may be manifested by increased activity, by increased growth, and by ECG and metabolic changes. In doubtful cases therapy may be withheld for a period in order to ascertain whether symptoms recur and biochemical changes regress.

The two commonly used drugs are L-thyroxine and tri-iodothyronine. The latter is 5 times as antigoitrogenic as thyroxine. Desiccated thyroid extract is not frequently used in this hospital because the results from it are variable owing to its unpredictable potency. Intravenous thyroxine produces a maximum response in the BMR within 7-10 days, whereas tri-iodothyronine provokes a maximum response in a matter of 24 hours. Both preparations produce a rapid and marked drop in the serum cholesterol.[19] Cessation of therapy may result in a return of the cholesterol to or beyond its former high level in 6 weeks.[12]

Conclusions from Present Cases

The patients described are presented here as examples of juvenile hypothyroidism. All the patients except case 2 gave positive histories of previous normal development up to a certain age. Case 2 had no witness to testify to early normal development, but one could infer from clinical examination and assessment of his ability to cope with his environment that his mental retardment was not great. In other words, one presumes on reasonable grounds that his thyroid production, although inadequate, was sufficient for him to develop, albeit sluggishly.

Even with the aid of modern laboratory methods, the precise aetiology of the disease in individual cases may remain unknown; sometimes it is quite obvious, as, for example, in case 5, who had suffered pituitary destruction by a craniopharyngioma. Case 3 had had a thyroid nodule in the neck which rapidly regressed on thyroid treatment; it is logical to conclude that she is probably an example of partial athyreosis, particularly because of the subsequent progress and behaviour of the nodule, the exogenous thyroid 'damping' the pituitary and allowing the stressed and hypertrophied remnant to subside.

When there is no thyroid tissue palpable, as in cases 1 and 4, the problem is more difficult. If there is no history of previous goitre or of thyroiditis or operation, the aetiology may not be discovered.

Radio-active iodine studies may or may not be helpful.

SUMMARY

Five cases of juvenile hypothyroidism are presented, together with classification and discussion of multiple causative factors.

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